

## Part B: Experimental Design and Protocol

### Human Subjects Protocol Application:

#### **Title: A Pilot Study of Dexmedetomidine-Propofol in Children Undergoing Magnetic Resonance Imaging**

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#### **Please provide a brief Summary or abstract of this research protocol.**

A recent publication in the New England Journal of Medicine highlighted the accumulating evidence for neurotoxic effects of anesthetics in animal models and a collection of epidemiologic studies in humans. Many of these studies are supported by the group Strategies for Mitigating Anesthesia-Related Neurotoxicity (SMARTTOTS). Recent studies of anesthesia in fetal and neonatal primates are yielding more evidence of neurotoxicity associated with many common anesthesia and sedation techniques (e.g. propofol, etomidate, sevoflurane, desflurane and isoflurane). On the other hand, the data suggest that some alternative sedative agents, such as Dexmedetomidine, may not have the same neurotoxic effect. Funding agencies and advocacy groups such as SmartTots along with the FDA and the American Academy of Pediatrics have concluded that the current data from these animal studies are sufficiently convincing that large scale clinical studies are warranted[1] .

Children routinely undergo sedation for MRI scanning with large doses of propofol and other sedatives. Many of these scans occur at young ages when these children may be at risk of neurological injury from sedative exposure. In addition, these scans do not involve any stimulation - which could be protective against neurodegeneration.

We propose a pilot study to determine if a standard bolus dose and infusion of dexmedetomidine can significantly decrease the dose of propofol (infusion) required for accomplishing an MRI. Review of intra-procedural records reveals that the standard infusion rate for propofol at BCH for MRI scans is 250mcg/kg/min after a 2-4mg/kg bolus. Based on previous work with the combination of propofol with dexmedetomidine for other procedures, we propose a standard dose of dexmedetomidine (1 mcg/kg bolus followed by an infusion at 0.5 mcg/kg/hour). We will augment this sedation with propofol 2-3mg/kg titrated bolus followed by 100mcg/kg/min infusion which can also be titrated up or down to a maximum of 300mcg/kg/min to keep the blood pressure and heart rate within 30% of baseline levels.). Outcome metrics will include: 1) Percentage of patients where this combination yields a quiet sedated state compatible with accomplishing an MRI scan (eyes closed and no movement) 2) MRI pauses from patient movement 3) incidence of adverse events such as airway obstruction, desaturation in spite of

supplemental O2, bradycardia, hypotension, hypertension 4) time required for induction, time for emergence and recovery.

Because we are testing these techniques in patients undergoing MRI, the outcomes are free of confounders related to surgical techniques, which is often a problem in anesthesia and perioperative research.

We hypothesize that the use of low dose propofol with dexmedetomidine will be effective in patients undergoing MRI while sparing exposure to the high dose of the sedative.

## **1. Specific Aim/Objective**

Determine if the combination of dexmedetomidine (1mcg/kg followed by 0.5 mcg/kg/hour with propofol 2-3mg/kg titrated bolus followed by 100mcg/kg/min) is effective for sedation in pediatric patients undergoing a magnetic resonance imaging (MRI) scan.

## **2. Background and Significance**

The Food and Drug Administration and the International Anesthesia Research Society have formed a public-private partnership called SmartTots to address concerns about potential adverse effects of general anesthesia in young children. Along with other nonclinical studies, research on the use of propofol in fetal and neonatal macaque monkeys suggests that it causes apoptosis of neurons and oligodendrocytes. In contrast, dexmedetomidine has not been shown to be neurotoxic in the studies. Factors influencing the extent of injury include age at the time of drug exposure, and cumulative anesthetic dose. The group concluded that the evidence available from these animal models is “sufficiently convincing to warrant large scale clinical studies”. The report also offers some fundamental questions that might be answered through further study including how much injury risk is attributable to the anesthesia as opposed to inflammatory processes or underlying disease and to consider whether strategies or interventions can be developed to reduce harm. [1]

Propofol and dexmedetomidine are both routinely used for sedation in children undergoing MRI. Wu compared each and found that while dexmedetomidine did not perform as well as propofol in terms of timeliness, effectiveness, it has been shown to be sufficiently effective [2]. Compared to other GABA inhibitors, propofol has a shorter induction time, shorter emergence, fewer interruptions during the scan, and shorter duration of stay in the PACU. Heard and colleagues did a series of case reviews of dexmedetomidine in pediatric MRI scans and similarly found that cases where dexmedetomidine was used alone, it was unpredictable with respect to adequate dosing or the duration of recovery but also noted that the addition of propofol to dexmedetomidine control inadequate sedation with no side effects, and even suggested the combination significantly increased the duration of effect than the use of propofol alone [3]. Triltsch et

al. studied the ability of dexmedetomidine to reduce propofol requirements in adult ICU patients and found it to be effective in that respect [4].

We believe that by studying the use of propofol-dexmedetomidine in children undergoing MRI scans we can shed light on some of the fundamental questions raised in the SmartTots report. Primarily we hope to explore whether a combination of propofol-dexmedetomidine is effective for sedation in pediatric patients undergoing a magnetic resonance imaging (MRI) scan. Because MRI scans are painless and non-invasive, sedation outcomes can be observed independent of any effects of pain or “inflammatory processes”.

### **3. Design and Methods**

#### **3a. Patient Selection and Inclusion/Exclusion Criteria**

##### **Inclusion Criteria:**

1. Subjects presenting as out-patients, scheduled to receive an anesthetic for MRI of brain, body (spine, chest, abdomen, and/or pelvis) and/or extremity (arm and/or leg).
2. The subject must be a candidate for the sedation technique described in this study with a natural airway (see exclusion criteria described below). This decision will be made by a staff member of the Department of Anesthesiology.
3. The subjects must be between 1 and 12 years of age.
4. The subject's legally authorized representative has given written informed consent to participate in the study.
5. ASA status I, II, or III

##### **Exclusion Criteria:**

1. The subject is an in-patient at BCH.
2. Diagnosis of a difficult airway or severe obstructive sleep apnea that is not compatible with spontaneous ventilation in a supine position.
3. Congenital heart disease or history of dysrhythmia.
4. Patient taking digoxin or beta-blocker
5. Anxiolytic medication is ordered before the MRI (e.g., midazolam or ketamine).
6. The subject has a history or a family (parent or sibling) history of malignant hyperthermia.

7. The subject is allergic to or has a contraindication to propofol or dexmedetomidine.
8. The subject has previously been treated under this protocol.
9. The subject has a tracheostomy or other mechanical airway device.
10. The subject has received within the past 12 hours an oral or intravenous alpha-adrenergic, beta-adrenergic agonist, or antagonist drugs (e.g., clonidine, propranolol, albuterol).
11. The subject is not scheduled to receive anesthesia-sedation care for the MRI.
12. The subject/family is not able to understand/speak English.

### 3b. Recruitment Methods

We plan to offer participation to patients aged between 1 and 12 years, who are scheduled for MRI at Boston Children's Hospital. Potentially eligible subjects will be identified through a review of the schedule of upcoming MRI scans, by age and scheduled procedure type. Potentially eligible patients will be sent a brochure describing our methodologies in lay language as well as a copy of the consent form, up to 1 month prior to their scheduled MRI. This brochure will include a link to a web-based, informational Power Point presentation. Potential participating families will be encouraged to view the presentation. Up to two weeks prior to the scheduled MRI scan, we will contact each potential participant by telephone to gauge their interest in participation and answer any questions concerning participation and/or the informational Power Point presentation. If the family agrees to participate a member of the study team will discuss the consent form and study process in further detail. If a family has not yet had an opportunity to view the informational slide show, and would like to do so, they will be able to view it at this time.

If a family agrees to participate in the study, their anesthesia team will be sent an email from the research team in advance of the MRI scan informing them of their patient's participation in the study.

### 3c. Description of Study Treatments or Exposures/Predictors

This is a prospective observational study of the use of propofol-dexmedetomidine for general anesthesia in pediatric patients undergoing an MRI scan. Eligible patients undergoing MRI scans, aged between 1 and 12 years, will be recruited from the MRI clinic at BCH and followed for the duration of their scan.

Based on previous work with the combination of propofol with dexmedetomidine for other procedures, we will begin by administering dexmedetomidine 1mcg/kg over 5 minutes. When this is completed, we will begin an infusion at 0.5 mcg/kg/hour. At the 5 minute point propofol will be given (2-3mg/kg titrated bolus followed by 100mcg/kg/min infusion). Sedation will be

scored as ‘yes’ or ‘no’ by the attending clinician depending on whether or not the child is in an adequate state to begin the MRI scan by ten minutes after starting this regimen. If the sedative effect of the dexmedetomidine-propofol does not produce a sedated state compatible with completing the MRI scan within 10 minutes, a repeat bolus of propofol 1-2mg/kg will be administered. The dose of DEX will not be changed. The 1-2mg/kg propofol dose will be repeated if the child is not adequately sedated in 2 more minutes. At this time infusion rate of propofol will be increased to 200 mcg/kg/minute. If the child is not sedated in 5 more minutes, the outcome will be recorded as a technique failure and sedation will continue at the discretion of the anesthesiologist.

A member of the research team will be present for the induction of the anesthesia. Either they or a second member of the clinical team will verify the doses and pump settings of the research medications specified above.

On the day of the participant’s scan, before the scan begins, demographic data will be collected – including age, weight, diagnosis, and coexisting medical conditions. This data will be obtained from the electronic medical record after enrollment in the study.

During the scan we will collect information on time to sufficient sedation, sedative consumption, the number of scan interruptions, hemodynamic information, the number and nature of any adverse events during the scan, length of scan. Per hospital standard of care, subjects will have blood pressure monitored by non-invasive blood pressure cuff every three minutes. End-tidal CO<sub>2</sub>, pulse-oximetry, and 3-lead-ECG monitoring will be monitored continuously and recorded every 5 minutes. Heart rate and respiratory rate will be continuously monitored and recorded every minute. Temperature will be recorded every 15 minutes.

Many safe-guards will be in place to protect patients while they are receiving sedation with dexmedetomidine and propofol. Subjects will receive standard anesthesia-level care, just as they would if they were not participating in the study. Board certified pediatric anesthesiologists will provide the care in the MRI suite at Boston Children’s Hospital along with a Certified Nurse Anesthetist, anesthesia resident, or pediatric anesthesia fellow. Per hospital standard operating protocol, patients will receive supplemental oxygen. There are anesthesia carts and code-carts fully stocked with a complete array of “code” medications as well as additional anesthetics, muscle relaxants etc.

After the scan is complete, when the participant is in the post anesthesia care unit (PACU) we will collect data on the number and nature of any adverse events (including any from the start of the study), emergence time, time to discharge criteria. Per hospital standard, patients are called the day after their procedure to assess for adverse events. Study staff will review the charts following this phone call to assess for adverse events following discharge from the hospital.

### 3d. Retention/Incentives

All participants will receive a thank you postcard from the study.

### 3e. Definition of Primary and Secondary Outcomes/Endpoints

#### *Primary outcomes:*

- Dosage/ consumption
  - Incidence of technique failure defined as lack of adequate sedation for MRI scan in spite of the sedation as described above.
- Incidence of patient movement and MRI interruption.
- Incidence of adverse events defined as: arterial desaturation, airway obstruction, hypotension and bradycardia.
- Incidence of agitation on emergence as defined by a PAED score of 10 or greater at any point during PACU stay.
- Times: Time from initiation of DEX infusion to meeting sedation criteria for MRI scan, duration of infusions of DEX and propofol, time in MRI suite, time to eye opening, time to full responsiveness, time to “ready for PACU discharge”.

### 3f. Data Collection Methods, Assessments, Interventions, and Schedule

Data will be collected from several resources:

1. Data on safety outcomes and Dexmedetomidine-Propofol consumption will be collected from the AIMS record (during the scan) and the electronic medical record (during recovery) and entered into an InForm database by members of the research team.
2. Data on incidence of MRI scan interruption will be observed directly by designated members of the research team and documented on a CRF
3. Time data for time to produce sedation, drug administration, duration of infusion, time to emergence, agitation (yes/no), time to ready for PACU discharge will be recorded by members of the research team and entered into the InForm database.

### 3g. Study Timeline

For the purpose of this pilot observational study, 30 eligible patients undergoing MRI scans, aged between 1 and 12 years, will be recruited from the MRI clinic at BCH and followed for the duration of their scan. It is expected that recruitment will be completed within 12 months from the start of the study.

## **4. Adverse Event Criteria and Reporting Procedures**

Adverse or unanticipated events will be reported as required to the Boston Children’s Hospital IRB according to institutional reporting requirements. A case report form will be used to document adverse events. Dexmedetomidine in the doses used in this study is not associated with

adverse respiratory events. We believe that the only adverse events that could reasonably be attributed to dexmedetomidine would be cardiovascular in nature. Adverse events will be evaluated using the WHO-UMC causality assessment system. Moderate adverse events will be defined as abnormal cardiovascular parameters including: 1) bradycardia greater than 30% below age-defined criteria, 2) hypertension of greater than 30% above age-defined criteria, or 3) hypotension greater than 30% below age-defined criteria, as defined by the values in the following tables [5].

<b>Normal Blood Pressure by Age (mmHg)</b>			
<b>Age</b>	<b>Systolic Pressure</b>	<b>Diastolic Pressure</b>	<b>Systolic Hypotension</b>
Toddler (1-2 y)	86-106	42-63	<70 + (age in years x 2)
Preschooler (3-5 y)	89-112	46-72	<70 + (age in years x 2)
School-age (6-9 y)	97-115	57-76	<70 + (age in years x 2)
Preadolescent (10-11 y)	102-120	61-80	<90
Adolescent (12-15 y)	110-131	64-83	<90

<b>Normal Heart Rate by Age (beats/minute)</b>		
<b>Age</b>	<b>Awake Rate</b>	<b>Sleeping Rate</b>
Neonate (<28 d)	100-205	90-160
Toddler (1-2 y)	98-140	80-120
Preschool (3-5 y)	80-120	65-100
School-age (6-11 y)	75-118	58-90
Adolescent (12-15 y)	60-100	50-90

If any of these hemodynamic profiles occur for a sustained period of more than one minute during the bolus or infusion of dexmedetomidine, the patient will be immediately withdrawn from the study and care will proceed at the discretion of the board-certified anesthesiologist after stopping dexmedetomidine. If adverse events occur after the infusion of dexmedetomidine is completed, the patient will be closely monitored and cared for at the discretion of the anesthesiologist.

Severe adverse effects will be considered life-threatening arrhythmias or loss of spontaneous circulation. If three moderate adverse events or one severe adverse event occur, the study will be stopped and the event will be reported to all necessary officials.

## **5. Data Management and Statistical Analysis**

### **5a. Data Management Methods**

Each subject will be assigned a unique identifier. An InForm database will be created to store data captured on case report forms and to collect survey data. InForm is a secure, web-based application designed to support electronic data capture for research. Only authorized users are permitted access to the data files, and daily server back-up activities are executed to ensure data recovery. The data capture screens will mimic the case report forms to promote accurate data entry. Paper files will be stored in locked cabinets in the office of the PI. Procedures to ensure

accurate and reliable data collection will include well designed data forms and training in data collection methods.

#### 5b. Quality Control Method

Data quality control will be assured through automated and manual methods. The study database enhances data quality through required entry fields for critical data and automatic flags for missing or out-of-range data. Case report forms are designed to closely mirror the format of data entry fields in the database to reduce risk of data transfer errors.

#### 5c. Data Analysis Plan

- Patient characteristics—frequency-gender, types of scan, mean/SD ages and weight, mean/SD length of scan, changes in hemodynamics (baseline against lowest recorded).
- Raw data will be recorded on the number of children in the study who have to stop the scan will be recorded. Furthermore, if a child's scan is stopped, the number of times their scan must be stopped and duration of scan delay will also be recorded.
- Raw data will be recorded on the number of children who experience a complication or adverse event during the MRI scan and/ or recovery. Raw data will be collected on the number of each type of complication.
- Raw data will be recorded for dosage and summary statistics will be reported for dosage.
- Compare patient characteristics, scan interruptions, complications against dosage/consumption.

#### 5d. Statistical Power and Sample Considerations

This is a pilot study. As such, we are not performing a power analysis to determine a required sample size. We plan to enroll 30 subjects for this pilot study.

#### 5e. Study Organization

The principal investigator for this study is Dr. Joseph Cravero in the Department of Anesthesiology, Perioperative and Pain Medicine at Boston Children's Hospital.

#### 5f. Data and Safety Monitoring Plan

The Data and Safety Monitoring Plan will focus on adequacy of data collection, and occurrence of serious adverse events. Subjects will be monitored by the Principal Investigator (Dr. Cravero). Any serious adverse events that occur will be promptly reported to the Institutional Review Board at Children's Hospital Boston according to IRB guidelines. A case report form will be used to document adverse events. The PI will



review the safety and progress of this study on a regular basis. All data that is to be released to investigators will be reviewed prior to release to ensure maintenance of confidentiality. An interim analysis will be performed following the enrollment of the first 15 participants.

## **6. Risk and Discomfort**

The use of propofol-dexmedetomidine is used as part of standard care at Boston Children's Hospital. There are no additional risks to standard care to participants in this research study, as study participants will have an MRI done with sedation regardless of study participation or non-participation. While some concerns have been raised regarding propofol the possibility of neural-apoptosis, the exposure to this medication will not be different based on a choice of participation or non-participation. In addition, dexmedetomidine has been suggested (in animal models) to confer some protection from neural-apoptosis and therefore participation may actually represent some benefit.. Although dexmedetomidine is not FDA approved for use in children, if parents choose not to have their children participate in this study it is still possible that their child may receive dexmedetomidine. In neonatal and infant animals, sedative and anesthetic agents, like propofol, produce adverse effects on brain development, including loss of brain cells resulting in long-term, possibly permanent changes in learning and behavior. These adverse effects appear to occur mostly after prolonged periods of sedation or anesthesia (generally greater than 3 hours) and when brain development is occurring at a rapid rate (which roughly occurs in children under 3 years of age). It is not known if similar adverse effects occur in humans. As a study participant you should be advised that the drugs we must provide to accomplish the procedure your child needs may have the potential to increase the loss of nerve cells in the developing brain of your child and that the clinical significance of any such changes is not known. There are some animal studies that suggest dexmedetomidine may be better than other anesthetics for a growing infant's brain. However, the effects of dexmedetomidine alone or in combination with propofol on the developing brain have not been thoroughly tested to date.

Patients will be removed from the study at any point if the attending physician feels that treatment with propofol-dexmedetomidine may be inappropriate to that patient's care at that time or they develop any of the exclusion criteria. If a patient enrolled in the study should have an adverse event and the reaction is severe or life-threatening, then the patient will be withdrawn from the study. If the adverse event is felt to be caused by the dexmedetomidine or propofol-dexmedetomidine combination, then the IRB and FDA will be notified of the adverse event.

## **7. Potential Benefits**

We believe that by studying the use of propofol-dexmedetomidine in children undergoing MRI scans we can shed light on some of the fundamental questions raised in the SmartTots report. Primarily we hope to explore whether a combination of propofol-dexmedetomidine is effective

for sedation in pediatric patients undergoing a magnetic resonance imaging (MRI) scan. The potential benefits of this study include a reduction in propofol dose and the opportunity to protect neurocognitive development in the pediatric population.

## **8. Privacy Provisions**

Information will only be made available to individuals who are part of the research team. Any results from tests performed for research purposes will not be placed in the medical record. Medical information collected for this study will only become part of the child's medical record if the information is determined to be pertinent to the care the child receives at Boston Children's Hospital. Disclosure of personal information may occur only when required by law.

## **9. Confidentiality Provisions**

All paper records are kept in locked cabinet with access restricted to the investigators. The study tablet is encrypted, password protected, and compliant with Boston Children's Hospital policies. When not in use it will be stored in a locked cabinet with access restricted to the investigators. No data will be stored directly on the device.

All identifying information such as dates of birth, names or medical record numbers, will be removed from the Anesthesia Oracle database instance. All patients will be assigned to an ID number that will be not linked to any patient identifying information. Research related data will not be entered in to patients' medical records. All data will be electronically secured in a private folder and password protected. Only research investigators and personnel affiliated with the study will have access to patient information.

An InForm database will be created to store data captured on case report forms and to collect remote survey data. InForm is a secure, web-based application designed to support electronic data capture for research. Only authorized users are permitted access to the data files, and daily server back-up activities are executed to ensure data recovery.

## **10. References**

1. Rappaport, B.A., et al., *Anesthetic Neurotoxicity — Clinical Implications of Animal Models*. New England Journal of Medicine, 2015. **372**(9): p. 796-797.
2. Wu, J., et al., *Comparison of propofol and dexmedetomidine techniques in children undergoing magnetic resonance imaging*. Paediatr Anaesth, 2014. **24**(8): p. 813-8.
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4. Triltsch, A.E., et al., *Bispectral index-guided sedation with dexmedetomidine in intensive care: a prospective, randomized, double blind, placebo-controlled phase II study*. Crit Care Med, 2002. **30**(5): p. 1007-14.

5. 2015 American Heart Association Guidelines: Update for Cpr and Ecc. Dallas, Texas: American Heart Association, 2015. Accessed August 8, 2016